IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Case No. 99,423)

In re: U.S. Patent No. 6,403,567	)
	)
Issue Date: June 11, 2002	)
	)
Inventors: Zablocki et al.	)
	)
Serial No. 09/338,185	)
	)
Filed: June 22, 1999	)
	)
For: N-Pyrazole A2A Receptor Agonists	)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450
Attention Certificate of Corrections Branch

REQUEST FOR CERTIFICATE OF CORRECTION
PURSUANT TO 37 C.F.R. § 1.322

Dear Sir:

The assignee of record of the above-captioned patent respectfully requests correction of the patent as indicated on the enclosed Form PTO-1050. In particular, correction of the following office mistake is requested:

At column 17, line 56, delete "4N" and replace with - - 4-yl)-N --

The mistake being corrected herein is a printing mistake made by the Patent Office.

Respectfully submitted,
McDONNELL BOEHNEN
HULBERT & BERGHOFF LLP

Date: June 23, 2008

By: /A. Blair Hughes/
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Reg. No. 32,901

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PTO/SB/44 (09-07)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 6403567

APPLICATION NO.: 09/338,185

ISSUE DATE: : June 11, 2002

INVENTOR(S) : Zablocki et al.

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

At column 17, line 56, delete "4N" and replace with - - 4-yl)-N --

MAILING ADDRESS OF SENDER (Please do not use customer number below):
A. Blair Hughes
McDonnell Boehnen Hulbert & Berghoff LLP
300 S. Wacker Drive
Chicago, IL 60606

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(MBHB Case No. 99-423)

In the Patent of:		
Jeff A. Zablocki et al.		Group Art Unit: 1623
Patent No.	6,403,567	Examiner: L. Crane
Issued:	June 11, 2002	Confirmation No. 1072
Serial No.	09/338,185	
Filed:	June 22, 1999	
For:	N-Pyrazole A2A Adenosine Receptor Agonists	

REQUEST FOR CERTIFICATE OF CORRECTION
PURSUANT TO 37 C.F.R. § 1.323

Attention Certificate of Corrections Branch
Commissioner for Patents
P.O. Box 1450
Alexandria Virginia 22313-1450

Sir:

This is a request for issuance of the accompanying Certificate of Correction pursuant to 35 U.S.C. § 255 and 1.323. The Assignee of Record, CV THERAPEUTICS, INC., seeks to correct a mistake of a clerical nature and of a minor character in the above-identified patent.

On February 19, 2002 the Applicant submitted a Response to the October 31, 2001 Final Rejection for the above-identified patent. A copy of the Reply is attached to this Request at Appendix A. Beginning at page 7 of the Reply, the applicants submitted pages of the specification marked up to show their proposed amendments. The specification changes included amending the name of the compound identified in Example 5 as well as adding the

numeric designation 12 after the tem "Compound" in Example 5 (See page 10).[1] A clean version of the amended specification pages was also attached to the Reply. Due to a clerical mistake, the entire first sentence of Example 5 was omitted from the clean version of the specification at page 27 of the Reply. The published patent included the Example 5 text and Figures set forth in the clean version of the specification pages attached at Appendix A including the clerical error. The assignee now wishes to correct this clerical error by reinserting the first sentence of Example 5 into the patent.

The correction requested is as follows:

At column 17, line 62, before the word "The" add the sentence Compound 12 (0.05 mg, 0.12 mmol) was added to 4 mL methylamine (40% sol. in water).

It is respectfully submitted that the error being corrected is an apparent clerical error. Moreover, the correction does not add new matter to the application nor does it necessitate reexamination of the application.

The Assignee authorizes the Commissioner to charge any underpayment or credit any overpayment to Deposit Account No. 13-2490.

Enclosed is a complete Certificate of Correction for U.S. Patent No. 6,403,567 issued June 11, 2002.

Consideration of this Request and issuance of the Certificate of Correction are respectfully requested.

Requested submitted,

Dated: June 23, 2008

/A. Blair Hughes/
A. Blair Hughes
Registration No. 32,901

[1] The addition of the number 12 was superfluous as Example 5 had been previously amended on June 11, 2001 to add the numeral 12 to the first sentence of Example 5.

APPENDIX A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Case No. 99-423)

In the Application of:		)	
		)	
	Jeff A. Zablocki, et al.	)	Examiner: L. Crane
		)	
Serial No.:	09/338,185	)	Group Art Unit: 1623
		)	
Filed:	June 22, 1999	)	
		)	
Title:	N-Pyrazole A_{2A} Receptor Agonists	)	

Asst. Commissioner for Patents
Washington, D.C. 20231

RESPONSE TO THE OCTOBER 31, 2001 FINAL REJECTION

Dear Sir:

Responsive to the Final Rejection dated October 31, 2001, please amend the above-referenced patent application as follows:

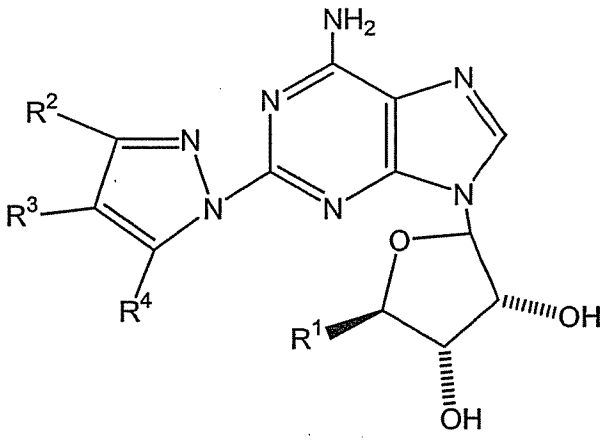
IN THE SPECIFICATION:

Cancel pages 24-28 from the application and replace with new pages 24-28 which are included at the end of this response.

IN THE CLAIMS:

Cancel claims 2-7, 13-18 and 28 from the application without prejudice.

1. (Twice amended) A compound having the formula:



wherein R^1 is $-CH_2OH$;

R^2 and R^4 are each hydrogen;

R^3 is selected from the group consisting of CO_2R^{20}, $-CONR^7R^8$ and aryl wherein the aryl substituent is optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, C_{1-6} alkyl, CF_3 and OR^{20};

R^7 is selected from the group consisting of hydrogen, C_{1-8} alkyl and aryl, wherein the alkyl and aryl substituents are optionally substituted with one substituent selected from the group consisting of halo, aryl, CF_3, CN, and OR^{20} and wherein each optional aryl substituent is optionally substituted with at least one substituent selected from the group consisting of halo, alkyl, CF_3 CN, and OR^{20};

R^8 is selected from the group consisting of hydrogen and C_{1-8} alkyl; and

R^{20} is selected from the group consisting of hydrogen and C_{1-8} alkyl.

8. (Twice amended) The compound of claim 1 wherein R^3 is selected from the group consisting of CO_2R^{20}, $-CONR^7R^8$, and aryl that is optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, C_{1-3} alkyl, CF_3 and OR^{20};

R^7 is selected from the group consisting of hydrogen, and C_{1-8} alkyl that is optionally substituted with one substituent selected from the group consisting of halo, CF_3, CN and OR^{20} ;

R^8 is selected from the group consisting of hydrogen and C_{1-3} alkyl; and

R^{20} is selected from the group consisting of hydrogen and C_{1-4} alkyl.

9. (Twice amended) The compound of claim 1 wherein R^3 is selected from the group consisting of CO_2R^{20}, $-CONR^7R^8$, and aryl that is optionally substituted with one substituent selected from the group consisting of halo, C_{1-3} alkyl, and OR^{20};

R^7 is selected from the group consisting of hydrogen, and C_{1-3} alkyl that is optionally substituted with one substituent selected from the group consisting of halo, CF_3, CN and OR^{20};

R^8 is hydrogen; and

R^{20} is selected from the group consisting of hydrogen and C_{1-4} alkyl.

10. (Twice amended) The compound of claim 1 wherein R^3 is selected from the group consisting of CO_2R^{20}, $-CONR^7R^8$, and aryl that is optionally substituted with one substituent selected from the group consisting of halo, C_{1-3} alkyl and OR^{20};

R^7 is selected from the group consisting of hydrogen, and C_{1-3} alkyl;

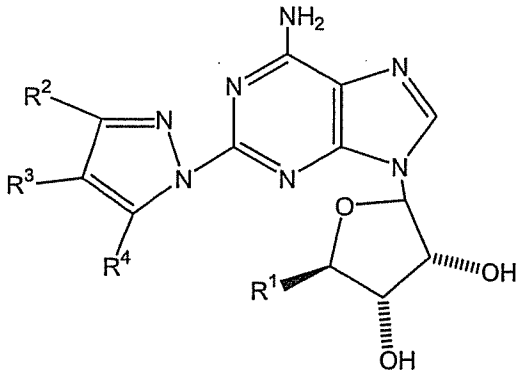
R^8 is hydrogen; and

R^{20} is selected from the group consisting of hydrogen and C_{1-4} alkyl.

23. (Twice amended) A pharmaceutical composition comprising the compound of claim 1 and one or more pharmaceutical excipients.

26. (Once amended) The compound of claim 1 selected from the group consisting of 2-(4-methylaminocarbonylpyrazol-1-yl)adenosine; 2-(4-ethoxycarbonylpyrazol-1-yl)adenosine; 2-[4-(4-chlorophenyl)pyrazol-1-yl)]adenosine; 2-[4-(4-methoxyphenyl)pyrazol-1-yl)]adenosine; 2-[4-(4-methylphenyl)pyrazol-1-yl)]adenosine; and 2-(4-carboxypyrazol-1-yl)adenosine.

27. (Once Amended) A compound having the following formula:



wherein R^1 is $-CH_2OH$;

R^2 and R^4 are each hydrogen;

R^3 is $-CONR^7R^8$;

R^7 is methyl; and

R^8 is hydrogen.

REMARKS

Claims 1, 8-12, 20-24 and 26-27 are pending in this application. The application claims have been amended to clarify the scope of the Applicants' invention in response to the Examiner's § 112 rejections. These amendments have also reduced the number of compounds that fall within the scope of the claimed invention. These claim amendments are made without prejudice to Applicant's right to seek a patent on the cancelled subject matter by way of a continuing application.

The application Examples and claim 26 have been amended to replace the incorrect adenosine nomenclature introduced in Applicant's June 11, 2001 Reply with the proper adenosine nomenclature for the compounds of this invention identified in Examples 1-7. Claim 27 has been converted from a dependent claim into an independent claim in the Reply as well.

The specification and claim amendments described above do not add new matter to the application.

By way of review, the Applicants have discovered a new class of 2-adenosine N-Pyrazole compositions that are useful as adenosine receptor agonists and that are particularly useful as A_{2A} receptor agonists.

The Examiner's claim objections are overcome as discussed below.

I. Claims 26 and 28

The Examiner did not consider newly submitted claims 26 and 28 because they were deemed to be distinct in scope from the invention originally claimed.

Claim 26 has been amended to name each of the compounds synthesized in Examples 1-7 using adenosine nomenclature. Claim 28 has been cancelled from this application without prejudice. The compounds of claim 26 were originally presented in cancelled claim 19 using IUPAC nomenclature. Therefore the amendment to claim 26 does not add new matter to the application.

II. Adenosine Nomenclature

The Applicants acknowledge that the adenosine nomenclature added to the specification and claims in the June 11, 2001 Reply is incorrect. Examples 1-7 and claim 26 have been amended to incorporate the correct adenosine nomenclature for the compounds whose chemical structure and IUPAC name appear in those Examples and in original claim 19.

III. 1-18, 20-24 and 27 – 112, First Paragraph Rejection

The Examiner rejected claims 1-18, 20-24 and 27 under 35 U.S.C. § 112 ¶ 1 as containing subject matter which is not described in the specification. More specifically, it is the Examiner's position that claim 1 is directed to a vast array of compounds which are not all

enabled by the specification.

The Applicants disagree with the rejection of all pending claims under the first paragraph of Section 112. In order to facilitate an early allowance of at least some of the application claims, however, the Applicants have narrowed the scope of compounds falling within the scope of the claims to those compounds actually made in the Examples and closely related compounds. This amendment to the claims is made without prejudice to the Applicant's rights to seek a patent of the cancelled subject matter by way of a continuing application.

IV. The Section 112, Second Paragraph Rejection of Claims 1 and 23

The Examiner identified several problems with the nomenclature used in claims 1 and 23. The problematic language has either been cancelled from the claims by this amendment or the claims at issue have been amended in the manner suggested by the Examiner.

V. Claim 27

Claim 27 has been converted from a dependent claim to an independent claim in this Reply. Claim 27 is drawn to Compound 16 of application Example 5. Since the compound of claim 27 was synthesized by the Applicants, the Examiner's Section 112, first paragraph claim rejection does not apply to the claim and claim 27 is believed to be allowable.

In view of the amendments and arguments presented above, it is believed that pending claims 1, 8-12, 20-24 and 26-27 of this application are allowable and that all rejections and objections should be withdrawn. Favorable reconsideration and allowance of the application claims is, therefore, courteously solicited.

Dated: February 19, 2002

By 

A Blair Hughes
Reg. No. 32,901
312-913-2123

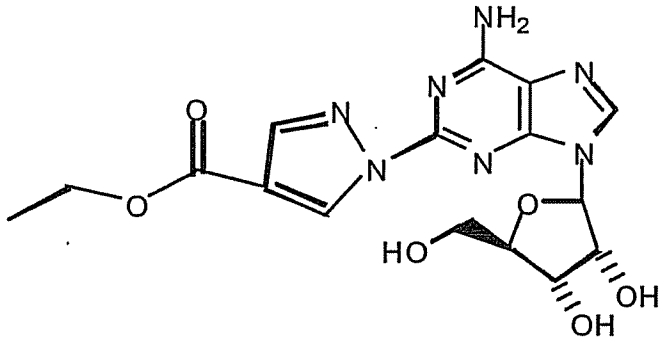
APPENDIX A

MARKED UP SPECIFICATION PARAGRAPHS AND CLAIMS PURSUANT TO 37 CFR 1.121 TO ACCOMPANY THE RESPONSE TO THE OCTOBER 31, 2001 OFFICAL ACTION

IN THE SPECIFICATION

Cancel pages 24-28 from the application and replace with new pages 24-28 which are attached hereto. The changes to specification pages 24-28 are set forth below.

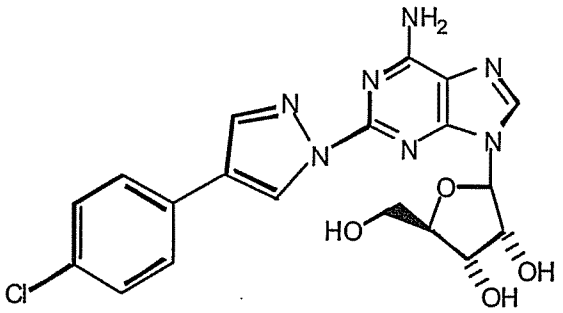
Example 1



Ethyl 1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazole-4-carboxylate which can also be identified as [N^6-{3-(3R)tetrahydrofuranyl}-2-(N-1-(4-ethoxycarbonyl)pyrazolyl)adenosine] 2-(4-ethoxycarbonylpyrazol-1-yl)adenosine (12).

To a suspension of 2-hydrazinoadenosine (0.025 g, 0.08 mmol) in a 1:1 mixture of MeOH/AcOH was added (ethoxycarbonyl)malondialdehyde ((0.019 g, 0.12 mmol) and the mixture was heated [heated] at 80^0C for 3 h. The precipitate formed was collected by filtration and washed with EtOH and ether to afford 12. ^{1}HNMR (DMSO-d6) δ1.25 (t, 3 H), 3.5 (m, 1 H), 3.6 (m, 1 H), 3.8 (d, 1 H), 4.15 (d, 1 H), 4.55 (m, 1H), 5.0 (t, 1 H), 5.2 (d, 1 H), 5.5 (d, 1 H), 5.9 (d, 1H), 7.15-7.3 (m, 5 H), 7.8 (br s, 2 H), 8.1 (s, 1H), 8.4 (s, 1 H), 8.9 (s, 1H).

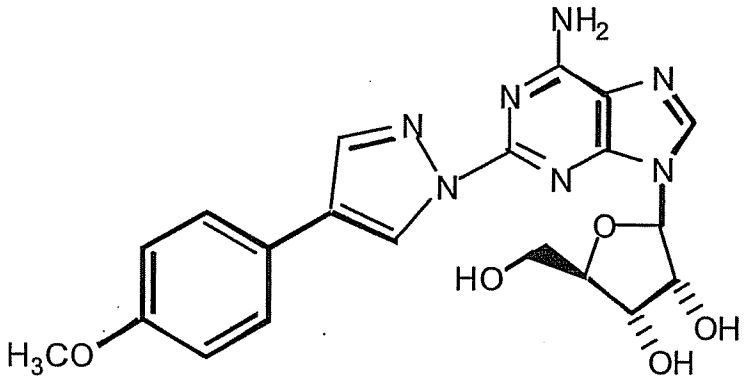
Example 2



(4S,2R,3R,5R)-2-{6-amino-2-[4-(4-chlorophenyl)pyrazolyl]purin-9-yl}-5-(hydroxymethyl)oxolane-3,4-diol which can also be identified as [N^6-{3-(3R)tetrahydrofuranyl}-2-(N-1-(4-(4-chlorophenyl))pyrazolyl)adenosine] 2-[4-(4-chlorophenyl)pyrazol-1-yl)]adenosine (13).

To a suspension of 2-hydrazinoadenosine (0.025 g, 0.08 mmol) in a 1:1 mixture of MeOH/AcOH was added 2-(4-chloro)malondialdehyde (0.022g, 0.12 mmol) and the mixture was heated at 80 ^{0}C for 3 h. The precipitate formed was collected by filtration and washed with EtOH and Ether to afford **13**. ^{1}HNMR (DMSO-d*6*) δ3.5 (m, 1 H), 3.6 (m, 1 H), 3.8 (d, 1 H), 4.15 (d, 1 H), 4.2 (q, 2 H), 4.55 (m, 1H), 5.9 (d, 1H), 7.45 (d, 2 H), 7.75 (d , 2 H), 8.25 (s, 1H), 8.35 (s, 1 H), 8.9 (s, 1H).

Example 3

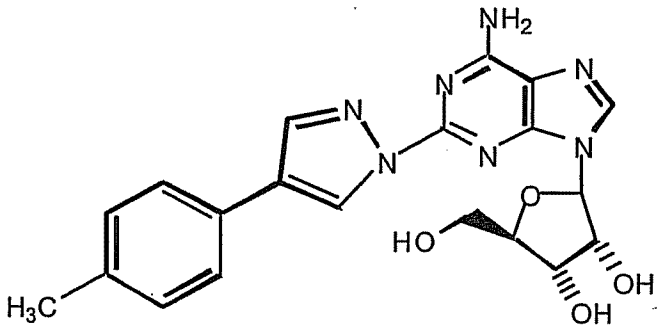


(4S,2R,3R,5R)-2-{6-amino-2-[4-(4-methoxyphenyl)pyrazolyl]purin-9-yl}-5-

(hydroxymethyl)oxolane-3,4-diol which can also be identified as [N^6-{3-(3R)tetrahydrofuranyl}-2-(N-1-(4-(4-methoxyphenyl))pyrazolyl)adenosine] 2-[4-(4-methoxyphenyl)pyrazol-1-yl)]adenosine (14).

To a suspension of 2-hydrazinoadenosine (0.025 g, 0.08 mmol) in a 1:1 mixture of MeOH/AcOH was added 2-(4-methoxy)malondialdehyde (0.022g, 0.12 mmol) and the mixture was heated at 80 ^{0}C for 3 h. The precipitate formed was collected by filtration and washed with EtOH and Ether to afford 14. ^{1}HNMR (DMSO-d*6*) δ3.55 (m, 1 H), 3.65 (m, 1 H), 3.75 (s, 3 H), 3.9 (d, 1 H), 4.15 (d, 1 H), 4.6 (m, 1 H), 5.9 (d, 1 H), 6.75 (d, 2 H), 7.6 (d , 2 H), 8.15 (s, 1H), 8.35 (s, 1 H), 8.8 (s, 1 H).

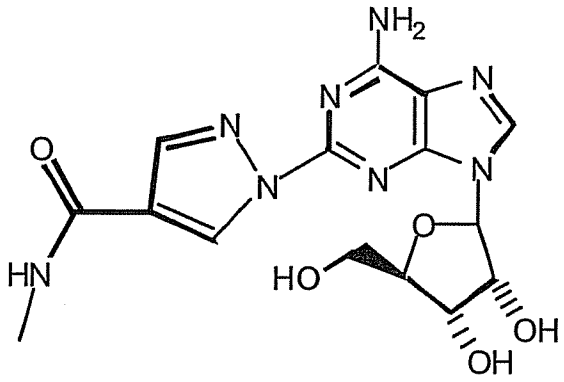
Example 4



(4S,2R,3R,5R)-2-{6-amino-2-[4-(4-methylphenyl)pyrazolyl]purin-9-yl}-5-(hydroxymethyl)oxolane-3,4-diol which can also be identified as [N^6-{3-(3R)tetrahydrofuranyl}-2-(N-1-(4-(4-methylphenyl))pyrazolyl)adenosine] 2-[4-(4-methylphenyl)pyrazol-1-yl)]adenosine (15).

To a suspension of 2-hydrazinoadenosine (0.025 g, 0.08 mmol) in a 1:1 mixture of MeOH/AcOH was added 2-(4-methyl)malondialdehyde (0.019g, 0.12 mmol) and the mixture was heated at 80 ^{0}C for 3 h. The precipitate formed was collected by filtration and washed with EtOH and Ether to afford **15**. ^{1}HNMR (DMSO-d*6*) δ3.55 (m, 1 H\), 3.65 (m, 1 H), 3.75 (s, 3 H),

3.9 (d, 1 H), 4.15 (d, 1 H), 4.6 (m, 1 H), 5.9 (d, 1 H), 6.75 (d, 2 H), 7.6 (d , 2 H), 8.15 (s, 1 H), 8.35 (s, 1 H), 8.8 (s, 1 H).

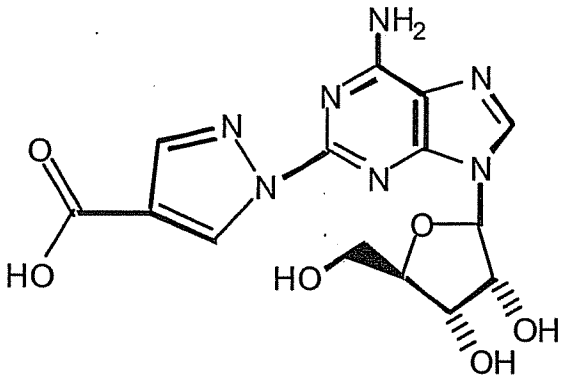


Example 5

(1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazol-4-yl)-N-methylcarboxamide which can also be identified as [N^6-{3-(3R)tetrahydrofuranyl}-2-(N-1-(4-methylaminocarbonyl)pyrazolyl)adenosine] 2-(4-methylaminocarbonylpyrazol-1-yl)adenosine (16).

Compound 12 (0.05 mg, 0.12 mmol) was added to 4 mL methylamine (40% sol. In water). The mixture heated at 65 ^{0}C in for 24 h. After concentration in vacuo, the residue was purified using prep. TLC (10% MeOH:DCM). ^{1}HNMR (CD_3OD) δ2.90 (s, 3 H), 3.78 (m, 1 H), 3.91 (m, 1 H), 4.13 (d, 1 H), 4.34 (d, 1 H), 4.64 (m, 1 H), 6.06 (d, 1 H), 8.11 (s, 1 H), 8.38 (s, 1 H), 9.05 (s, 1 H).

Example 6



1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazole-4-carboxylic acid which can also be identified as [N^6-{3-(3R)tetrahydrofuranyl}-2-(N-1-(4-carboxy)pyrazolyl)adenosine] 2-(4-carboxypyrazol-1-yl)adenosine (17).

Compound 12 (0.05 mg, 0.12 mmol) was dissolved one equivalent of 1N NaOH. The solution was allowed to stir at Rt for 2h, then acidified to pH 4. The resulting precipitate was filtered and washed with water and ether. ^{1}HNMR (CD_3OD) Δ3.75 (m, 1 H), 3.90 (m, 1 H), 4.13 (d, 1 H), 4.43 (d, 1 H), 4.64 (m, 1H), 6.05 (d, 1H), 8.10 (s, 1H), 8.35 (s, 1 H), 9.05 (s, 1 H).

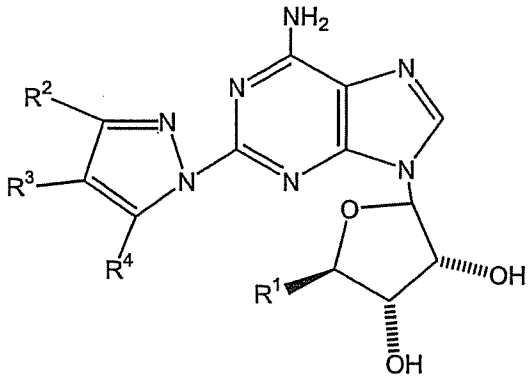
Example 7

Compositions of this invention were assayed to determine their affinity for the A2A receptor in a pig striatum membrane prep. Briefly, 0.2 mg of pig striatal membranes were treated with adenosine deaminase (2 U/ mL) and 50 mM Tris buffer (pH = 7.4) followed by mixing. To the pig membranes was added 2 μL of serially diluted DMSO stock solution of the compounds of this invention at concentrations ranging from 10 nM to 100 microM or the control received 2 microL of DMSO alone, then the trotted antagonist ZM 241385 in Tris buffer (50 mM, pH of 7.4) was added to achieve a final concentration of 2 nM . After incubation at 23 ° C for 2h, then the solutions were filtered using a membrane harvester using multiple washing of the membranes

(3 x). The filter disks were counted in scintillation cocktail to determine the amount of displacement of tritiated ZM displaced by the compositions of this invention. Greater than a 5 point curve was used to generate Ki's. and the number of experiments is indicated in the column marked in Table 1 below.

IN THE CLAIMS

1. (Twice amended) A compound having the formula:



wherein R^1 [=] is $-CH_2OH$[, or $-CONR_5R_6$];

R^2 and R^4 are each hydrogen;

R^3 is selected from the group consisting of CO_2R^{20}, $-CONR^7R^8$ and aryl wherein the aryl substituent is optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, C_{1-6} alkyl, CF_3 and OR^{20} [C_{1-15} alkyl, halo, NO_2, CF_3, CN, OR^{20}, SR^{20}, $N(R^{20})_2$, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, $SO_2NR^{20}COR^{22}$, $SO_2NR^{20}CO_2R^{22}$, $SO_2NR^{20}CON(R^{20})_2$, $N(R^{20})_2$ $NR^{20}COR^{22}$, $NR^{20}CO_2R^{22}$, $NR^{20}CON(R^{20})_2$, $NR^{20}C(NR^{20})NHR^{23}$, COR^{20}, CO_2R^{20}, $CON(R^{20})_2$, $CONR^{20}SO_2R^{22}$, $NR^{20}SO_2R^{22}$, $SO_2NR^{20}CO_2R^{22}$, $OCONR^{20}SO_2R^{22}$, $OC(O)R^{20}$, $C(O)OCH_2OC(O)R^{20}$, and $OCON(R^{20})_2$,$-CONR^7R^8$, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl, and heteroaryl, wherein the alkyl, alkenyl, alkynyl, aryl, heterocyclyl and heteroaryl substituents are optionally substituted with from 1 to 3 substituents independently

selected from the group consisting of halo, alkyl, NO_2, heterocyclyl, aryl, heteroaryl, CF_3, CN, OR^{20}, SR^{20}, $N(R^{20})_2$, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, $SO_2NR^{20}COR^{22}$, $SO_2NR^{20}CO_2R^{22}$, $SO_2NR^{20}CON(R^{20})_2$, $N(R^{20})_2$ $NR^{20}COR^{22}$, $NR^{20}CO_2R^{22}$, $NR^{20}CON(R^{20})_2$, $NR^{20}C(NR^{20})NHR^{23}$, COR^{20}, CO_2R^{20}, $CON(R^{20})_2$, $CONR^{20}SO_2R^{22}$, $NR^{20}SO_2R^{22}$, $SO_2NR^{20}CO_2R^{22}$, $OCONR^{20}SO_2R^{22}$, $OC(O)R^{20}$, $C(O)OCH_2OC(O)R^{20}$, and $OCON(R^{20})_2$ and wherein the optional heteroaryl, aryl, and heterocyclyl substituent is optionally substituted with one or more substituents selected from the group consisting of halo, NO_2, alkyl, CF_3, amino, monoalkylamino, dialkylamino, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, $NCOR^{22}$, $NR^{20}SO_2R^{22}$, COR^{20}, CO_2R^{20}, $CON(R^{20})_2$, $NR^{20}CON(R^{20})_2$, $OC(O)R^{20}$, $OC(O)N(R^{20})_2$, SR^{20}, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, CN, and OR^{20};

R^5 and R^6 are each individually selected from the group consisting of H, and C_1-C_{15} alkyl optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, NO_2, heterocyclyl, aryl, heteroaryl, CF_3, CN, OR^{20}, SR^{20}, $N(R^{20})_2$, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, $SO_2NR^{20}COR^{22}$, $SO_2NR^{20}CO_2R^{22}$, $SO_2NR^{20}CON(R^{20})_2$, $N(R^{20})_2$ $NR^{20}COR^{22}$, $NR^{20}CO_2R^{22}$, $NR^{20}CON(R^{20})_2$, $NR^{20}C(NR^{20})NHR^{23}$, COR^{20}, CO_2R^{20}, $CON(R^{20})_2$, $CONR^{20}SO_2R^{22}$, $NR^{20}SO_2R^{22}$, $SO_2NR^{20}CO_2R^{22}$, $OCONR^{20}SO_2R^{22}$, $OC(O)R^{20}$, $C(O)OCH_2OC(O)R^{20}$, and $OCON(R^{20})_2$ and wherein the optional heteroaryl, aryl, and heterocyclyl substituent are optionally substituted with one or more substituents selected from the group consisting of halo, NO_2, alkyl, CF_3, amino, monoalkylamino, dialkylamino, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, $NCOR^{22}$, $NR^{20}SO_2R^{22}$, COR^{20}, CO_2R^{20}, $CON(R^{20})_2$, $NR^{20}CON(R^{20})_2$, $OC(O)R^{20}$, $OC(O)N(R^{20})_2$, SR^{20}, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, CN, and OR^{20};

R^7 is selected from the group consisting of hydrogen, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15}

alkynyl, heterocyclyl, aryl and heteroaryl, wherein the alkyl, alkenyl, alkynyl, aryl, heterocyclyl and heteroaryl substituents are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, NO_2, heterocyclyl, aryl, heteroaryl, CF_3, CN, OR^{20}, SR^{20}, $N(R^{20})_2$, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, $SO_2NR^{20}COR^{22}$, $SO_2NR^{20}CO_2R^{22}$, $SO_2NR^{20}CON(R^{20})_2$, $N(R^{20})_2$ $NR^{20}COR^{22}$, $NR^{20}CO_2R^{22}$, $NR^{20}CON(R^{20})_2$, $NR^{20}C(NR^{20})NHR^{23}$, COR^{20}, CO_2R^{20}, $CON(R^{20})_2$, $CONR^{20}SO_2R^{22}$, $NR^{20}SO_2R^{22}$, $SO_2NR^{20}CO_2R^{22}$, $OCONR^{20}SO_2R^{22}$, $OC(O)R^{20}$, $C(O)OCH_2OC(O)R^{20}$ and $OCON(R^{20})_2$ and wherein the optional heteroaryl, aryl and heterocyclyl substituents are optionally substituted with one or more substituents selected from the group consisting of halo, NO_2, alkyl, CF_3, amino, monoalkylamino, dialkylamino, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, $NCOR^{22}$, $NR^{20}SO_2R^{22}$, COR^{20}, CO_2R^{20}, $CON(R^{20})_2$, $NR^{20}CON(R^{20})_2$, $OC(O)R^{20}$, $OC(O)N(R^{20})_2$, SR^{20}, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, CN, and OR^{20};

R^8 is selected from the group consisting of hydrogen, $C_{1\text{-}15}$ alkyl, $C_{2\text{-}15}$ alkenyl, $C_{2\text{-}15}$ alkynyl, heterocyclyl, aryl, and heteroaryl, wherein the alkyl, alkenyl, alkynyl, aryl, heterocyclyl, and heteroaryl substituents are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, NO_2, heterocyclyl, aryl, heteroaryl, CF_3, CN, OR^{20}, SR^{20}, $N(R^{20})_2$, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, $SO_2NR^{20}COR^{22}$, $SO_2NR^{20}CO_2R^{22}$, $SO_2NR^{20}CON(R^{20})_2$, $N(R^{20})_2$ $NR^{20}COR^{22}$, $NR^{20}CO_2R^{22}$, $NR^{20}CON(R^{20})_2$, $NR^{20}C(NR^{20})NHR^{23}$, COR^{20}, CO_2R^{20}, $CON(R^{20})_2$, $CONR^{20}SO_2R^{22}$, $NR^{20}SO_2R^{22}$, $SO_2NR^{20}CO_2R^{22}$, $OCONR^{20}SO_2R^{22}$, $OC(O)R^{20}$, $C(O)OCH_2OC(O)R^{20}$, and $OCON(R^{20})_2$ and wherein each optional heteroaryl, aryl, and heterocyclyl substituent is optionally substituted with one or more substituents selected from the group consisting of halo, NO_2, alkyl, CF_3, amino, monoalkylamino, dialkylamino, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, $NCOR^{22}$, $NR^{20}SO_2R^{22}$,

COR^{20}, CO_2R^{20}, $CON(R^{20})_2$, $NR^{20}CON(R^{20})_2$, $OC(O)R^{20}$, $OC(O)N(R^{20})_2$, SR^{20}, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, CN, and OR^{20};

R^{20} is selected from the group consisting of H, C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl, and heteroaryl, wherein the alkyl, alkenyl, alkynyl, heterocyclyl, aryl, and heteroaryl substituents are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, alkyl, monoalkylamino, dialkylamino, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, CN, O-C_{1-6} alkyl, CF_3, aryl, and heteroaryl;

R^{22} is selected from the group consisting of C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl, and heteroaryl, wherein the alkyl, alkenyl, alkynyl, heterocyclyl, aryl, and heteroaryl substituents are optionally substituted with from 1 to 3 substituents independently selected from the group consisting of halo, alkyl, monoalkylamino, dialkylamino, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, CN, O-C_{1-6} alkyl, CF_3, aryl, and heteroaryl; and

wherein R^2 and R^4 are selected from the group consisting of H, C_{1-6} alkyl, and aryl that is optionally substituted with halo, CN, CF_3, OR^{20} and $N(R^{20})_2$, with the proviso that when R^2 is not hydrogen then R^4 is hydrogen, and when R^4 is not hydrogen then R^2 is hydrogen.]

R^7 is selected from the group consisting of hydrogen, C_{1-8} alkyl and aryl, wherein the alkyl and aryl substituents are optionally substituted with one substituent selected from the group consisting of halo, aryl, CF_3, CN, and OR^{20} and wherein each optional aryl substituent is optionally substituted with at least one substituent selected from the group consisting of halo, alkyl, CF_3 CN, and OR^{20};

R^8 is selected from the group consisting of hydrogen and C_{1-8} alkyl; and

R^{20} is selected from the group consisting of hydrogen and C_{1-4} alkyl.

8. (Twice amended) The compound of claim 1 wherein [R^1 is $-CH_2OH$;]

R^3 is selected from the group consisting of CO_2R^{20}, $-CONR^7R^8$, and aryl that is optionally substituted with from 1 to 2 substituents independently selected from the group consisting of halo, C_{1-3} alkyl, CF_3 and OR^{20};

R^7 is selected from the group consisting of hydrogen, and C_{1-8} alkyl that is optionally substituted with one substituent selected from the group consisting of halo, CF_3, CN and OR^{20} ;

R^8 is selected from the group consisting of hydrogen and C_{1-3} alkyl; and

R^{20} is selected from the group consisting of hydrogen and C_{1-4} alkyl.

9. (Twice amended) The compound of claim 1 wherein [R^1 is $-CH_2OH$;]

R^3 is selected from the group consisting of CO_2R^{20}, $-CONR^7R^8$, and aryl that is optionally substituted with one substituent selected from the group consisting of halo, C_{1-3} alkyl, and OR^{20};

R^7 is selected from the group consisting of hydrogen, and C_{1-3} alkyl that is optionally substituted with one substituent selected from the group consisting of halo, CF_3, CN and OR^{20};

R^8 is hydrogen; and

R^{20} is selected from the group consisting of hydrogen and C_{1-4} alkyl.

10. (Twice amended) The compound of claim 1 wherein [R^1 is $-CH_2OH$;]

R^3 is selected from the group consisting of CO_2R^{20}, $-CONR^7R^8$, and aryl that is optionally substituted with one substituent selected from the group consisting of halo, C_{1-3} alkyl and OR^{20};

R^7 is selected from the group consisting of hydrogen, and C_{1-3} alkyl;

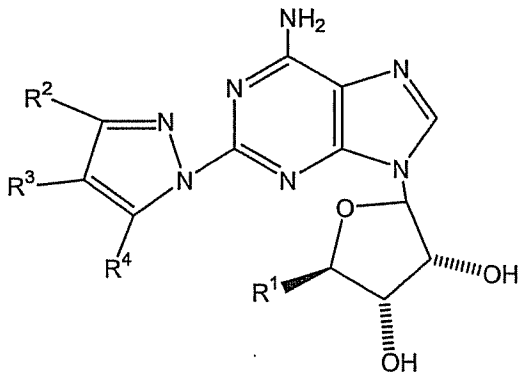
R^8 is hydrogen; and

R^{20} is selected from the group consisting of hydrogen and C_{1-4} alkyl.

23. (Once amended) A pharmaceutical composition comprising the [composition] compound of claim 1 and one or more pharmaceutical excipients;

26. (Once amended) The compound of claim 1 selected from the group consisting of [N^6-{3-(3R)tetrahydrofuranyl}-2-(N-1-(4-ethoxycarbonyl)pyrazolyl)adenosine; N^6-{3-(3R)tetrahydrofuranyl}-2-(N-1-(4-(4-chlorophenyl))pyrazolyl)adenosine; N^6-{3-(3R)tetrahydrofuranyl}-2-(N-1-(4-(4-methoxyphenyl))pyrazolyl)adenosine; N^6-{3-(3R)tetrahydrofuranyl}-2-(N-1-(4-(4-methylphenyl))pyrazolyl)adenosine; N^6-{3-(3R)tetrahydrofuranyl}-2-(N-1-(4-methylaminocarbonyl)pyrazolyl)adenosine; and N^6-{3-(3R)tetrahydrofuranyl}-2-(N-1-(4-carboxy)pyrazolyl)adenosine] 2-(4-methylaminocarbonylpyrazol-1-yl)adenosine; 2-(4-ethoxycarbonylpyrazol-1-yl)adenosine; 2-[4-(4-chlorophenyl)pyrazol-1-yl)]adenosine; 2-[4-(4-methoxyphenyl)pyrazol-1-yl)]adenosine; 2-[4-(4-methylphenyl)pyrazol-1-yl)]adenosine; and 2-(4-carboxypyrazol-1-yl)adenosine.

27. (Once Amended) [The] A compound [of claim 10] having the following formula:



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wherein R^1 is $-CH_2OH$;

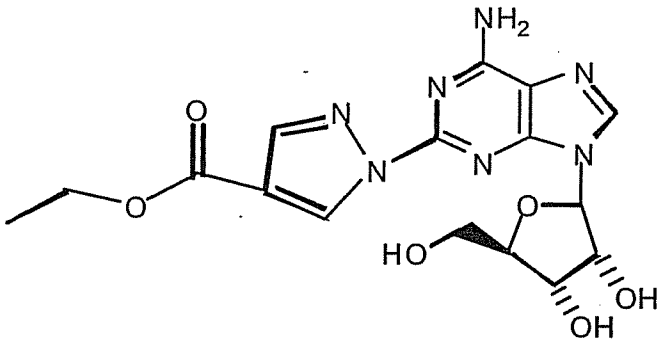
R^2 and R^4 are each hydrogen;

R^3 is $-CONR^7R^8$;

R^7 is methyl; and

R^8 is hydrogen.

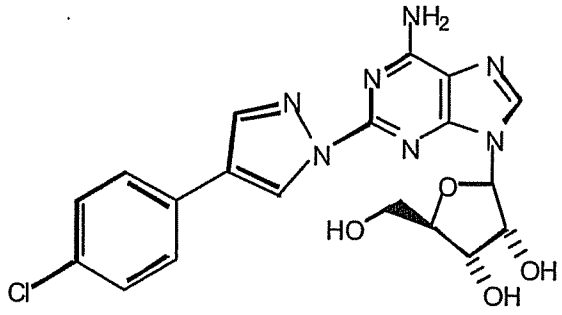
Example 1



Ethyl 1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazole-4-carboxylate which can also be identified as 2-(4-ethoxycarbonylpyrazol-1-yl)adenosine (12).

To a suspension of 2-hydrazinoadenosine (0.025 g, 0.08 mmol) in a 1:1 mixture of MeOH/AcOH was added (ethoxycarbonyl)malondialdehyde ((0.019 g, 0.12 mmol) and the mixture was heated [heated] at 80^0C for 3 h. The precipitate formed was collected by filtration and washed with EtOH and ether to afford 12. ^{1}HNMR (DMSO-dδ) δ1.25 (t, 3 H), 3.5 (m, 1 H), 3.6 (m, 1 H), 3.8 (d, 1 H), 4.15 (d, 1 H), 4.55 (m, 1H), 5.0 (t, 1 H), 5.2 (d, 1 H), 5.5 (d, 1 H), 5.9 (d, 1H), 7.15-7.3 (m, 5 H), 7.8 (br s, 2 H), 8.1 (s, 1H), 8.4 (s, 1 H), 8.9 (s, 1H).

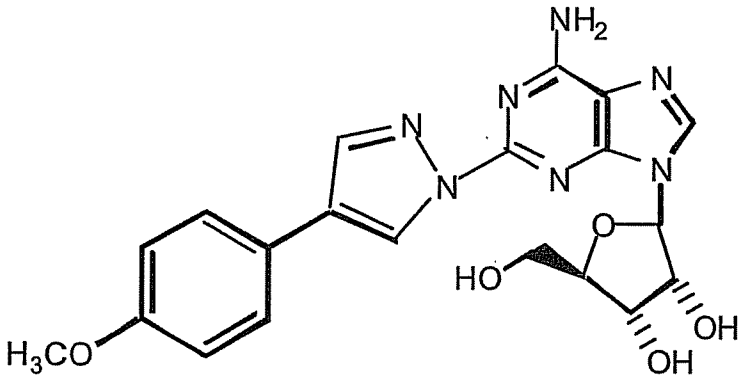
Example 2



(4S,2R,3R,5R)-2-{6-amino-2-[4-(4-chlorophenyl)pyrazolyl]purin-9-yl}-5-(hydroxymethyl)oxolane-3,4-diol which can also be identified as 2-[4-(4-chlorophenyl)pyrazol-1-yl)]adenosine (13).

To a suspension of 2-hydrazinoadenosine (0.025 g, 0.08 mmol) in a 1:1 mixture of MeOH/AcOH was added 2-(4-chloro)malondialdehyde (0.022g, 0.12 mmol) and the mixture was heated at 80 ^{0}C for 3 h. The precipitate formed was collected by filtration and washed with EtOH and Ether to afford **13**. ^{1}HNMR (DMSO-d*6*) δ3.5 (m, 1 H), 3.6 (m, 1 H), 3.8 (d, 1 H), 4.15 (d, 1 H), 4.2 (q, 2 H), 4.55 (m, 1H), 5.9 (d, 1H), 7.45 (d, 2 H), 7.75 (d , 2 H), 8.25 (s, 1H), 8.35 (s, 1 H), 8.9 (s, 1H).

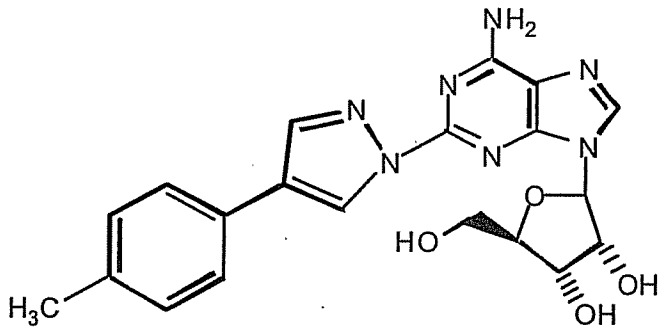
Example 3



(4S,2R,3R,5R)-2-{6-amino-2-[4-(4-methoxyphenyl)pyrazolyl]purin-9-yl}-5-(hydroxymethyl)oxolane-3,4-diol which can also be identified as 2-[4-(4-methoxyphenyl)pyrazol-1-yl)]adenosine (14).

To a suspension of 2-hydrazinoadenosine (0.025 g, 0.08 mmol) in a 1:1 mixture of MeOH/AcOH was added 2-(4-methoxy)malondialdehyde (0.022g, 0.12 mmol) and the mixture was heated at 80 ^{0}C for 3 h. The precipitate formed was collected by filtration and washed with EtOH and Ether to afford 14. ^{1}HNMR (DMSO-d*6*) δ3.55 (m, 1 H), 3.65 (m, 1 H), 3.75 (s, 3 H), 3.9 (d, 1 H), 4.15 (d, 1 H), 4.6 (m, 1 H), 5.9 (d, 1 H), 6.75 (d, 2 H), 7.6 (d , 2 H), 8.15 (s, 1H), 8.35 (s, 1 H), 8.8 (s, 1 H).

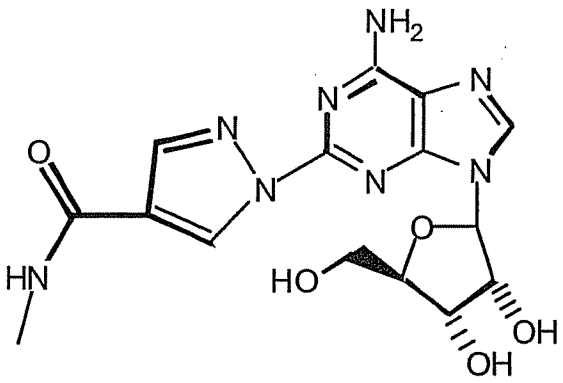
Example 4



(4S,2R,3R,5R)-2-{6-amino-2-[4-(4-methylphenyl)pyrazolyl]purin-9-yl}-5-(hydroxymethyl)oxolane-3,4-diol which can also be identified as 2-[4-(4-methylphenyl)pyrazol-1-yl)]adenosine (15).

To a suspension of 2-hydrazinoadenosine (0.025 g, 0.08 mmol) in a 1:1 mixture of MeOH/AcOH was added 2-(4-methyl)malondialdehyde (0.019g, 0.12 mmol) and the mixture was heated at 80 ^{0}C for 3 h. The precipitate formed was collected by filtration and washed with EtOH and Ether to afford **15**. ^{1}HNMR (DMSO-d*6*) δ3.55 (m, 1 H\), 3.65 (m, 1 H), 3.75 (s, 3 H), 3.9 (d, 1 H), 4.15 (d, 1 H), 4.6 (m, 1 H), 5.9 (d, 1 H), 6.75 (d, 2 H), 7.6 (d , 2 H), 8.15 (s, 1 H), 8.35 (s, 1 H), 8.8 (s, 1 H).

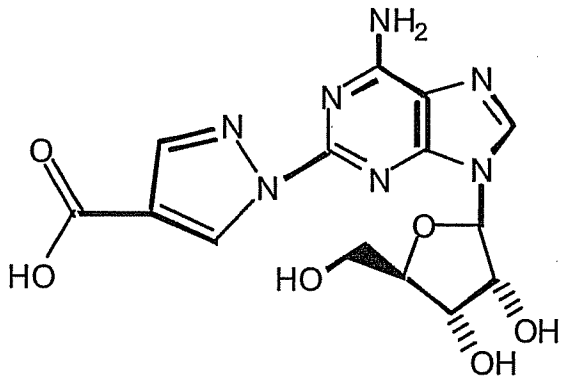
Example 5



(1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazol-4-yl)-N-methylcarboxamide which can also be identified as 2-(4-methylaminocarbonylpyrazol-1-yl)adenosine (16).

The mixture heated at 65 ^{0}C in for 24 h. After concentration in vacuo, the residue was purified using prep. TLC (10% MeOH:DCM). ^{1}HNMR (CD_3OD) δ2.90 (s, 3 H), 3.78 (m, 1 H), 3.91 (m, 1 H), 4.13 (d, 1 H), 4.34 (d, 1 H), 4.64 (m, 1 H), 6.06 (d, 1 H), 8.11 (s, 1 H), 8.38 (s, 1 H), 9.05 (s, 1 H).

Example 6



1-{9-[(4S,2R,3R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-6-aminopurin-2-yl}pyrazole-4-carboxylic acid which can also be identified as 2-(4-carboxypyrazol-1-yl)adenosine (17).

Compound 12 (0.05 mg, 0.12 mmol) was dissolved one equivalent of 1N NaOH. The solution was allowed to stir at Rt for 2h, then acidified to pH 4. The resulting precipitate was filtered and washed with water and ether. ^{1}HNMR (CD_3OD) Δ3.75 (m, 1 H), 3.90 (m, 1 H), 4.13 (d, 1 H), 4.43 (d, 1 H), 4.64 (m, 1H), 6.05 (d, 1H), 8.10 (s, 1H), 8.35 (s, 1 H), 9.05 (s, 1 H).

Example 7

Compositions of this invention were assayed to determine their affinity for the A2A receptor in a pig striatum membrane prep. Briefly, 0.2 mg of pig striatal membranes were treated with adenosine deaminase (2 U/ mL) and 50 mM Tris buffer (pH = 7.4) followed by mixing. To the pig membranes was added 2 μL of serially diluted DMSO stock solution of the compounds of this invention at concentrations ranging from 10 nM to 100 microM or the control received 2 microL of DMSO alone; then the trotted antagonist ZM 241385 in Tris buffer (50 mM, pH of 7.4) was added to achieve a final concentration of 2 nM . After incubation at 23 °C for 2h, then the solutions were filtered using a membrane harvester using multiple washing of the membranes (3 x). The filter disks were counted in scintillation cocktail to determine the amount of displacement of tritiated ZM displaced by the compositions of this invention. Greater than a 5 point curve was used to generate Ki's. and the number of experiments is indicated in the column marked in Table 1 below.

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(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 6403567

APPLICATION NO.: 09/338,185

ISSUE DATE: : June 11, 2002

INVENTOR(S) : Zablocki et al.

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

At column 17, line 62, before the word "The" add the sentence -- Compound 12 (0.05 mg, 0.12 mmol) was added to 4 mL methylamine (40% sol. in water). --

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